PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

EINGEGANGEN 18. Juni 2004

PCT10/506917

To:

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SUISSE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.06.2004
Applicant's or agent's file reference: E1103-WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CH 03/00153	05.03.2003	07.03.2002

Applicant
EIDGENÖSSISCHE TECHNISCHE HOCHSCHULE ZÜRICH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference E1103-WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CH 03/00153	International filing date *(day/month/year)* 05.03.2003	Priority date *(day/month/year)* 07.03.2002
International Patent Classification (IPC) or both national classification and IPC C12N9/10, C12N9/10		
Applicant EIDGENÖSSISCHE TECHNISCHE HOCHSCHULE ZÜRICH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.09.2003	16.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Lanzrein, M Telephone No. +49 89 2399-7358

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CH 03/00153

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-13 as originally filed

Claims, Numbers

1-13 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/CH 03/00153

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 9-13

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 9-13

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

No international search report was established for claims 9-13. Said claims are therefore not subject to the preliminary examination as set forth under Rule 66.1 (e) PCT.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application presents an *E. coli* expression system for production of N-glycosylated proteins. The campylobacter jejuni glycosylation machinery (pgl) was transferred into E. coli for this purpose. Recombinant AcrA protein was produced and glycosylation verified by mass spectroscopy.

2. Reference is made to the following documents:

   D1: SZYMANSKI C M ET AL: "EVIDENCE FOR A SYSTEM OF GENERAL PROTEIN GLYCOSYLATION IN CAMPYLOBACTER JEJUNI" MOLECULAR MICROBIOLOGY, BLACKWELL SCIENTIFIC, OXFORD, GB, vol. 32, no. 5, 1999, pages 1022-1030, XP008012013 ISSN: 0950-382X

   D2: WACKER M ET AL: "N-linked glycosylation in Campylobacter jejuni and its FUNCTIONAL TRANSFER INTO E.COLI" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 298, 29 November 2002 (2002-11-29), pages 1790-1793, XP002225920 ISSN: 0036-8075

2. **Priority**

   Since the priority document pertaining to the present application is not yet available to the IPEA, this Written Opinion has been drawn up considering the

priority date (7. 03. 2002) as valid. D2 (Wacker *et al.*) has been published between the priority date and the filing date of the present application. Thus, said document is not considered to constitute prior art in the meaning of Rule 64(1)(b) PCT. However, if it turns out that the effective date of the claimed subject-matter is not the priority date, then D2 will become relevant to assess whether the present application satisfies the criteria set forth in Art. 33(2) and (3) PCT.

3. **Novelty** (Art. 33 (2) PCT)

Claims 1-8 appear to be novel over the prior art cited in the ISR.

4. **Inventive Step**(Art. 33 (3) PCT)

D1 discloses the pgl locus in *C. jejuni* and its individual genes, including pglB as oligosaccharide transferase (Fig. 1B, table 1). The pgl genes were introduced into E. coli, which resulted in altered LPS cores and reactivity to O:23/O:36 serum (Fig. 2; p. 1024, left-hand column, paragraph 3). This result shows that the E. coli LPS had the C. jejuni oligosaccharide pattern upon transformation with the pgl locus.

D1 does not provide evidence for N-glycosylation and there is no teaching or evidence that foreign genes would be glycosylated by by the pglB cluster in E. coli. As D1 only shows alteration in LPS, from which it is not obvious to conclude that proteins would be glycosylated.

Therefore, the subject-matter of claims 1-8 is considered to involve an inventive step in the sense of Art. 33 (3) PCT.

5. **Clarity/Sufficiency of Disclosure** (Art. 6/5 PCT)

Claims 1-8 attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added (cf PCT Guidelines III 4.7).
On the one hand, it is obvious how to introduce genes or gene clusters into E. coli. On the other hand, claim 1 does not specify anything with regards to the

"metabolic apparatus". This term is very broad and the claim is not supported over the whole scope when considering only a single bacterial gene cluster is disclosed as an example of such a metabolic apparatus. Extension of the scope to any "metabolic apparatus" capable of carrying out the "requested N-glycosylation" is by no means warranted.

Moreover, sufficient disclosure is lacking (Art. 5 PCT) because the claims broadly extend to *any* metabolic apparatus capable of carrying out N-glycosylation, which is in contrast to the disclosure of only one single prokaryotic machinery (C. jejuni) that has been transferred into E. coli.
Selecting other metabolic systems for transfer into E. coli would require extensive testing with regards to the functionality of system (i.e. whether the system really produces glycosylated proteins), which amounts to an undue burden for the skilled person. It might indeed be very difficult to find any other bacterial glycosylation system suitable for the desired purpose when considering the following statement in D2: "To our knowledge, a general N-glycosylation system very similar to the one found in eukaryotes has not been described in other bacteria, and the C. jejuni genome is the only bacterial genome sequenced to date that harbors a gene that encodes a protein with strong sequence homology to a eukaryotic oligosaccharyltransferase component." (p. 1793, left-hand column, last paragraph).
Not only do the claims refer to any metabolic apparatus, but also to any "target protein", which is in stark contrast to the fact that only one protein, namely AcrA was shown to be glycosylated. It appears therefore that also the selection of target proteins amenable of being glycosylated represents undue burden to the person of average skill in the art.